Sofosbuvir/velpatasvir (Epclusa®) New Drug Update

July 2016

Drug Name:	**sofosbuvir/velpatasvir**
Trade Name (Manufacturer):	**Epclusa (Gilead)**
Form:	Tablets
Strength:	sofosbuvir 400 mg/velpatasvir 100 mg
FDA Approval:	June 28, 2016
Market Availability:	July 5, 2016
FDA Approval Classification:	Priority Review; Breakthrough Therapy
Classification:	Specific Therapeutic Class (HIC3): Hepatitis C Virus – NS5B Polymerase and NS5A Inhibitor Combinations (W0B)

INDICATION[1]

Sofosbuvir/velpatasvir (Epclusa) is a fixed-dose combination of sofosbuvir, a hepatitis C virus (HCV) nucleotide analog NS5B polymerase inhibitor, and velpatasvir, an HCV NS5A inhibitor. It is indicated for the treatment of adult patients with chronic HCV genotype 1, 2, 3, 4, 5 or 6 infection with or without compensated cirrhosis, or with decompensated cirrhosis in combination with ribavirin.

CONTRAINDICATIONS/WARNINGS

When sofosbuvir/velpatasvir is used in combination with ribavirin, contraindications and warnings of ribavirin will also apply.

Serious symptomatic bradycardia may occur in patients taking amiodarone, particularly in patients also receiving beta blockers or those with underlying cardiac comorbidities and/or advanced liver disease. Coadministration of amiodarone with sofosbuvir/velpatasvir is not recommended. In patients without alternative viable treatment options, cardiac monitoring, including initial monitoring in an inpatient setting, is recommended.

Sofosbuvir/velpatasvir also carries a warning regarding reduced efficacy when used concomitantly with P-glycoprotein (P-gp) inducers and/or moderate to potent inducers of cytochrome P450, specifically CYP2B6, CYP2C8, and CYP3A4. Concurrent use is not recommended.

DRUG INTERACTIONS

Sofosbuvir and velpatasvir are substrates of P-gp and breast cancer resistance protein (BCRP). Concomitant sofosbuvir/velpatasvir therapy with the following inducers of P-gp and/or moderate to potent inducers of CYP2B6, CYP2C8, or CYP3A4 may decrease the concentration of sofosbuvir/velpatasvir: efavirenz, phenytoin, phenobarbital, carbamazepine, oxcarbazepine, rifampin, rifabutin, rifapentine, St. John's wort, and tipranavir/ritonavir. Coadministration is not recommended.

Concomitant therapy with the following medications could decrease the concentration of sofosbuvir/velpatasvir due to decreased gastric pH: antacids (aluminum and magnesium hydroxide), H2-receptor antagonists, proton-

pump inhibitors (PPIs). Separate administration time of antacids by 4 hours. H2-receptor antagonists may be given simultaneously with sofosbuvir/velpatasvir or 12 hours apart at doses ≤ 40 mg twice daily of famotidine or the equivalent. If coadministration with a PPI is unavoidable (e.g., medically necessary), administer sofosbuvir/velpatasvir with food 4 hours prior to administration of omeprazole 20 mg; use with other PPIs has not been studied.

Concomitant therapy with amiodarone is not recommended due to the risk of serious symptomatic bradycardia as described above.

Velpatasvir is an inhibitor of drug transporters P-gp, BCRP, OATP1B1, OATP1B3, and OATP2B1. Concomitant therapy with sofosbuvir/velpatasvir could increase concentrations of the following interacting medications: digoxin, topotecan, tenofovir, HMG CoA reductase inhibitors (e.g., atorvastatin, rosuvastatin). Additional monitoring and/or dose adjustments of the concomitant agent may be required; coadministration with topotecan is not recommended.

COMMON ADVERSE EFFECTS

The most common adverse reactions (incidence ≥ 10%) observed with treatment with sofosbuvir/velpatasvir for 12 weeks were headache and fatigue. When combined with ribavirin for 12 weeks, the most common adverse reactions (incidence ≥ 10%) were fatigue, anemia, nausea, headache, insomnia and diarrhea.

SPECIAL POPULATIONS

Pregnancy

No adequate human data are available to establish whether or not sofosbuvir/velpatasvir poses a risk to pregnancy outcomes. Ribavirin is contraindicated in pregnant women and in men whose partners are pregnant.

Pediatrics

Safety and effectiveness of sofosbuvir/velpatasvir in patients younger than 18 years of age have not been established.

Geriatrics

No overall differences in safety or effectiveness were observed between subjects ≥ 65 years and younger subjects in clinical trials; however, greater sensitivity of some older individuals cannot be ruled out.

Hepatic/Renal Impairment

No dosage adjustment of sofosbuvir/velpatasvir is required for patients with mild, moderate, or severe hepatic impairment (Child-Pugh Class A, B, or C). Clinical and hepatic laboratory monitoring (including direct bilirubin), as clinically indicated, is recommended for patients with decompensated cirrhosis receiving treatment with sofosbuvir/velpatasvir and ribavirin.

No dosage adjustment of sofosbuvir/velpatasvir is required for patients with mild or moderate renal impairment. The safety and efficacy of sofosbuvir/velpatasvir have not been established in patients with severe renal impairment (eGFR less than 30 mL/min/1.73 m^2) or end-stage renal disease (ESRD) requiring hemodialysis.

DOSAGES

The recommended dose of sofosbuvir/velpatasvir is one tablet (400 mg sofosbuvir/ 100 mg of velpatasvir) orally once daily with or without food.

CLINICAL TRIALS [2,3,4]

*A literature search was conducted using "*sofosbuvir," "velpatasvir,*" and "hepatitis C".*

The efficacy and safety of sofosbuvir/velpatasvir in patients with chronic HCV infection were evaluated in 4 randomized, multicenter, phase 3 trials: the ASTRAL trials.

ASTRAL-1[5]: This randomized double-blind trial, evaluated treatment-naïve and treatment-experienced (prior interferon-containing regimen) patients (n=740) with genotype 1, 2, 4, 5, or 6 without cirrhosis or with compensated cirrhosis (Child-Pugh A). Patients were randomized 5:1 to either sofosbuvir/velpatasvir 400 mg/100 mg or placebo once daily for 12 weeks; however, all patients with genotype 5 were assigned sofosbuvir/velpatasvir due to the low prevalence of this genotype. In this trial, randomization was stratified according to the genotype and the presence or absence of cirrhosis. In the sofosbuvir/velpatasvir group (n=624), 34% of the patients had HCV genotype 1a, 19% genotype 1b, 17% genotype 2, 19% genotype 4, 6% genotype 5, and 7% genotype 6. Nineteen percent of the patients assigned sofosbuvir/velpatasvir had cirrhosis. The primary efficacy end point was the rate of sustained virologic response at 12 weeks after the end of treatment (SVR12). Overall, SVR12 among patients who received 12 weeks of sofosbuvir/velpatasvir was 99% (95% confidence interval [CI], 98 to > 99), which was significantly superior to the prespecified performance goal of 85% ($p<0.0001$). None of the 116 patients in the placebo group had a SVR. Rates of SVR were similar regardless of the HCV genotype: 98% in patients with genotype 1a infection, 99% with genotype 1b, 100% with genotype 2, 100% with genotype 4, 97% with genotype 5, and 100% with genotype 6. Nearly all of the patients with cirrhosis achieved SVR12 (all genotypes; 120/121; 99%). Only one of the patients in the sofosbuvir/velpatasvir group discontinued treatment prematurely because of an adverse event.

ASTRAL-2[6]: This open-label trial (n=266) compared sofosbuvir/velpatasvir 400/100 mg once daily (n=134) to sofosbuvir 400 mg with weight-based ribavirin for 12 weeks (n=132) in treatment-naïve and treatment-experienced (prior interferon-containing regimen) patients with genotype 2. Fourteen percent of those enrolled had cirrhosis while 15% were treatment-experienced. The overall SVR12, the primary outcome, in subjects who received sofosbuvir/velpatasvir and sofosbuvir with ribavirin was 99% (95% CI, 96 to 100) and 94% (95% CI, 88 to 97), respectively. There were no virologic failures among patients receiving sofosbuvir/velpatasvir despite the presence of NS5A and NS5B resistance-associated variants; however, in those receiving sofosbuvir with ribavirin, 6 patients (5%) had a virologic relapse and 2 were lost to follow-up.

ASTRAL-3[7]: This open-label trial (n=552) compared sofosbuvir/velpatasvir 400/100 mg once daily for 12 weeks (n=277) to sofosbuvir 400 mg with weight-based ribavirin for 24 weeks (n=275) in treatment-naïve and treatment-experienced (prior interferon-containing regimen) patients with genotype 3. Thirty percent of those enrolled had cirrhosis while 26% were treatment-experienced. The SVR12 rates in patients who received sofosbuvir/velpatasvir were 95% (95% CI, 92 to 98) compared to 80% (95% CI, 75 to 85) in those who received sofosbuvir with ribavirin.

ASTRAL-4[8]: An open-label trial, evaluated the efficacy of sofosbuvir/velpatasvir in treatment-naïve and treatment-experienced patients with genotypes 1 through 6 chronic HCV infection and decompensated cirrhosis (Child-Pugh B). Patients were randomized 1:1:1 to sofosbuvir/velpatasvir 400/100 mg once daily for 12 weeks, sofosbuvir/velpatasvir 400/100 mg once daily with ribavirin for 12 weeks, or sofosbuvir/velpatasvir 400/100 mg once daily for 24 weeks (n=267). Of those who received treatment, 78% were genotype 1, 4% were genotype 2, 15% were genotype 3, 3% were genotype 4, and <1% were genotype 6; while not excluded, no genotype 5 patients were enrolled. The median baseline Child-Pugh score was 8 (range, 5 to 10), median baseline Model for End-Stage Liver Disease (MELD) score was 10 (range, 6 to 24; majority ≤ 15). Overall SVR12 rates, the primary outcome, were 83% (95% CI, 74 to 90), 94% (95% CI, 87 to 98), and 86% (95% CI, 77 to 92) for the 12-week regimen of sofosbuvir/velpatasvir, the 12-week regimen of sofosbuvir/velpatasvir with ribavirin, and the 24-

week regimen of sofosbuvir/velpatasvir, respectively. Notably, SVR12 rates as low as 50% were reported in genotype 3 patients assigned sofosbuvir/velpatasvir for 12 or 24 weeks (no ribavirin).

OTHER DRUGS USED FOR CONDITION[9]

Other treatment options for patients with chronic HCV genotype 1 infections include daclatasvir (Daklinza™) with sofosbuvir (Sovaldi®), elbasvir/grazoprevir (Zepatier™) with or without ribavirin, ledipasvir/sofosbuvir (Harvoni®), ombitasvir/paritaprevir/ritonavir/dasabuvir (Viekira Pak™) with or without ribavirin, simeprevir (Olysio®) with ribavirin and peg-interferon, sofosbuvir with simeprevir (Olysio), and sofosbuvir and ribavirin with or without interferon.

Fewer treatment options are available for genotypes 2 through 6. The current primary treatment for patients with chronic HCV genotype 2 is sofosbuvir and ribavirin with or without interferon. Treatment options for genotype 3 chronic HCV infection are daclatasvir (Daklinza) with sofosbuvir (Sovaldi) or sofosbuvir (Sovaldi) and ribavirin with or without interferon. For patients with chronic HCV genotype 4 infection, treatments include elbasvir/grazoprevir (Zepatier), ledipasvir/sofosbuvir (Harvoni), ombitasvir/paritaprevir/ritonavir (Technivie™) with ribavirin, and sofosbuvir and ribavirin with or without interferon. The oral treatment for patients with chronic HCV genotype 5 or 6 infection is ledipasvir/sofosbuvir (Harvoni).

Regimen selection, duration of treatment, and use of ribavirin and/or interferon are dependent on treatment experience, degree of cirrhosis, HIV co-infection, renal impairment, and other patient specific factors.

PLACE IN THERAPY

Sofosbuvir/velpatasvir (Epclusa) is the first pangenotypic agent approved for chronic HCV. Sofosbuvir/velpatasvir offers an oral single tablet, fixed-dose 12-week treatment regimen for chronic HCV genotypes 1 to 6 in treatment-naïve and treatment-experienced patients without cirrhosis or with compensated cirrhosis (Child-Pugh A). In combination with ribavirin, sofosbuvir/velpatasvir also offers a 12-week option in patients with decompensated cirrhosis. Sofosbuvir/velpatasvir joins daclatasvir (Daklinza)/sofosbuvir (Sovaldi) and ledipasvir/sofosbuvir (Harvoni), as an option in patients with decompensated cirrhosis.

Sofosbuvir/velpatasvir has been studied in patients with HIV coinfection, but this is not a part of its labeling.[10]

There are several other agents available to treat genotype 1, the most common genotype in the US. Sofosbuvir/velpatasvir offers another all-oral, ribavirin-free choice in the treatment of this genotype. Sofosbuvir/velpatasvir provides a single tablet, ribavirin-free option for genotypes 2 and 3, the second most common genotypes in the US. Sofosbuvir/velpatasvir is also an option for genotypes 4, 5, and 6, although far less common in the US. Current options for genotype 4 include ledipasvir/sofosbuvir, sofosbuvir + ribavirin + interferon, ombitasvir/paritaprevir/ritonavir (Technivie) +/- ribavirin, and elbasvir/grazoprevir (Zepatier) +/- ribavirin. Ledipasvir/sofosbuvir is the only alternative for genotypes 5 and 6.

The American Association for the Study of Liver Diseases and Infectious Diseases Society of America (AASLD/IDSA) HCV Guidance has included sofosbuvir/velpatasvir in their recommendations for all genotypes as well as for off-label use in the HCV/HIV co-infection population.[11] In the US, current standard diagnostics and disease prognostics tests such as genotyping, fibrosis scores, liver function tests, renal function assessment, and HIV coinfection status will continue to remain a relevant part of practice.

SUGGESTED UTILIZATION MANAGEMENT

Anticipated Therapeutic Class Review (TCR) Placement	Hepatitis C Agents
Clinical Edit	Refer to HCV Pathways/Criteria
Quantity Limit	28 tablets/28 days
Duration of Approval	12 weeks

REFERENCES

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